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EXAMINER	
CARLSON	

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-138 are pending in the application.
   Of the above, claims 69-98, 101-138 are withdrawn from consideration.
2. ☒ Claims 2-24 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 25-68, 99, 100 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The numbering of claims is not accordance with 37 C.F.R. § 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 C.F.R. § 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Claims 2-24 have been cancelled. Misnumbered claims 2-112 have been renumbered 25-135, respectively.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1, 25-68, 99, and 100 (formerly Claims 1, 2-45, 76, 77), drawn to DNA encoding cystic fibrosis transmembrane conductance regulator, vectors, expression and therapeutic compositions, classified in Class 536, subclass 27.

II. Claims 69-86, 106, 107, 109, 111-121 (formerly Claims 46-63, 83, 84, 86, 88-98), drawn to CFTR and therapeutic compositions, classified in Class 530, subclass 350.

III. Claims 87-90 (formerly Claims 64-67), drawn to a method for treating CF with DNA, classified in Class 453, subclass 69.1.

IV. Claims 91-93 (formerly Claims 68-70), drawn to a method for treating CF with protein, classified in Class 514, subclass 8, 12.

V. Claims 94-96, formerly Claims 71-73), drawn to a method for screening using cell expressing CFTR DNA, classified in Class 435, subclass 7.2.

VI. Claims 97-98 (formerly 74-75), drawn to a method for assaying function via protein, classified in Class 435, subclass 7.1.

VII. Claims 101-105 (formerly Claims 78-82), drawn to a kit for assessing CFTR function via cells expressing CFTR, classified in Class 435, subclass 69.1.

VIII. Claims 108, 110, drawn to transgenic mice expressing CFTR, classified in Class 800, subclass 2.

IX. Claims 122-135, drawn to antibodies against CFTR, classified in Class 530, subclass 387.

The inventions are distinct, each from the other because of the following reasons:

The nucleic acids of Invention I are related to the protein of Invention II by virtue of encoding same. The DNA molecule has utility for the recombinant production of the protein in a host cell, as recited in the Claim. Although the DNA molecule and protein are related since the DNA encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay.

The protein of Invention II is related to the antibody of Invention IX by virtue of being the cognate antigen, necessary for the production of antibodies. Although the protein and antibody are related due to the necessary stearic complementarity of the two, they are distinct inventions because the protein can be used another and materially different process from the use for production of the antibody, such as in a pharmaceutical composition in its own right, or to assay or purify the natural ligand of the protein (if the protein is a receptor), or in assays for the identification of agonists or antagonists of the receptor protein.

The nucleic acid of Invention I and the antibody of Invention IX are related by virtue of the protein that is encoded by the nucleic acid and necessary for the production of the antibody. However, the nucleic acid itself is not necessary for antibody production and both are wholly different compounds having different compositions and functions. Therein, these Inventions are distinct.

Inventions I and III, V, VII, or VIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as either of the uses described in Inventions III, V, VII, or VIII.

Invention I and IV or VI are related by virtue that the DNA encodes the protein used in either of the methods. However, the DNA itself is not used in the methods of Inventions IV or VI and

the protein can be made synthetically as discussed above. Therein, Invention I is independent and distinct from these inventions.

Inventions II and IV or VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product as claimed can be used in a materially different process such as XX. either of the uses described in Inventions IV or VI or to make antibodies.

Inventions II and III, V, VII, or VIII are related in that the DNA encodes the protein of Invention II and is used in the methods of Inventions III, V, VII, and VIII. Invention II and III, V, VII, or VIII are distinct because the protein of Invention II is not used in any of the methods of Inventions III, V, VII, or VIII.

Inventions III, IV, V, and VI are related by virtue of the DNA and the protein as discussed above. Inventions III, IV, V, and VI are directed to methods comprising different, independent steps and are therein distinct.

Inventions VII, VIII, and IX are related to Inventions III, IV, V, and VI by virtue of the DNA used to make the mice and the kit as well as the protein to make the antibody. Inventions VII, VIII, and IX are distinct from Inventions III, IV, V, and VI because neither the kit, mice, or antibodies are used in the methods of Inventions III, IV, V, and VI.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Elizabeth Hanley on October 27, 1993, a provisional election was made with traverse to prosecute Invention I, claims 1, 25-68, 99, and 100. Affirmation of this election must be made by applicant in responding to this Office action. Claims 69-98 and 101-135 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The disclosure is objected to because of the following informalities: mistypes throughout the specification and claims. This same rejection has been made in Paper #2 and no attempts have been made to make any corrections. Appropriate correction is required.

Claims 1, 25-68, 99, and 100 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the DNA encoding the CFTR protein of Fig. 1. See M.P.E.P. §§ 706.03(n) and 706.03(z). Claims 1 and 36 are for any DNA encoding any CFTR and Claim 47 is for DNA encoding any CFTR activity. The specification only teaches how to make and use the CFTR disclosed and not other regulators of chloride current. It would require undue experimentation to determine proteins that are chloride regulatory channels other than CFTR, determine their activity, and acquire the DNA encoding the protein because it is not predictable what proteins are chloride channel regulators or if these proteins act in subunit form and are derived from different genes. Claim 50 is for any DNA comprising the synthetic "intron" in Fig. 6. The Claims should be limited to only that DNA encoding the CFTR or the synthetic intron of the instant invention and not other CFTR known or

unknown. It would require undue experimentation to determine DNA having such an intron and if that intron would render the host expression of the DNA silent because it is not predictable if the intron depicted in Fig. 6 is an exon in other proteins, such as observed in splicing.

Claims 35 and 40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 35 and 40 it is not clear what comprises a stabilizing agent or element for DNA and this term does not appear to be defined in the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

102e/103

Claims ~~1~~, ~~28~~, ~~30-33~~, ~~35~~, 36, 37, ~~40~~, 46-~~49~~, 55-57, ~~63, 64~~ 62-64, and ~~95-100~~ are rejected under 35 U.S.C. § 102(e) as being anticipated by Collins et al. (USP 5,240,846). Collins et al. teach vectors for the expression of the CFTR gene to used for gene therapy. Collins et al. deliver and express a single normal copy of the CFTR gene and this corrects the chloride regulatory defect in human colon tumor cell lines. Collins et al. teach silent mutations to stabilize the cloning of the gene (col. 3, 11). The transfer of the gene is by fusing the target cell to liposomes (col. 3, 15), plasmids, viral vectors, and retroviruses (col. 3). CFTR vectors are administered to the patient by injection, ingestion, or inhalation (col. 6).

Claims ~~1~~, 26, ~~28~~, ~~32~~, ~~35~~, ~~47~~, ~~48~~, 55-57, and 62-64 are rejected under 35 U.S.C. § 102(a) as being anticipated by Riordan et al. (1989). Riordan et al. cloned the CFTR gene from epithelial cells (Claims 1, 28, 32, 47, 48, 55-57, 62-64). Most of the cDNA isolated contained sequence insertions corresponding to introns ((Claims 26, 35; page 1067, col. 1). The DNA was in single copy form (page 1069, col. 1). Fig. 6 teaches the DNA and amino acid sequences coding CFTR and position 508 is starred to show where the common deletion of Phe is located in mutated CFTR. Therein, these Claims are anticipated by Riordan et al.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims ~~29~~, ~~34~~, ~~43~~ 44-45, 58, 60, 61, 65, 67, and 68 rejected under 35 U.S.C. § 103 as being unpatentable over Collins et al (USP 5,240,846). The teachings of Collins et al. are discussed above. Further, Collins et al. teach that the deletion of Phe at position 508 is the most common mutation in CFTR and CFTR defective cell lines can be used to diagnose CF and screen for carriers (col. 7). Though Collins et al. do not teach the vector of Claim 29, it would have been obvious to a person of ordinary skill in the art to make such a vector such that low copy numbers of CFTR are expressed because Collins et al. teach low copy vectors to prevent cell death during the expression of CFTR (col. 2). Collins et al. teach that the DNA encoding CFTR (col. 16+) and this sequence is nearly identical (99%) to that of the

instant application but for a single base change at nucleotide 1990. This single base change may be incidental. None-the-less, this changes the Applicants His to Asn at position 620, over 100 amino acids away from the known active region of CFTR at position 508. Therein, it would have been obvious to a person of ordinary skill in the art that these sequences encode the same protein (Claim 34). Collins et al. teach that the most common mutation occurs at amino acid position 508 with the deletion of Phe. Therein, it would have been obvious to a person of ordinary skill in the art to delete the DNA codon encoding amino acid position 508 in low copy vectors to express the mutated CFTR because Collins et al. teach the use of such systems for diagnosing CF (Claims 41-45). Collins et al. express the CFTR in mammalian cell lines rendering it obvious to a person of ordinary skill in the art to express CFTR in other mammalian cell lines such as CHO and C127 (Claims 58, 65). Collins et al. cloned the CFTR. Collins et al. do not teach that they cloned in E. coli though they did use appropriate vectors and promoters for cloning in E. coli. Therein, it would have been obvious to a person of ordinary skill in the art to express the CFTR gene in low copy vectors in E. coli because Collins et al. most likely cloned expressed CFTR in low copy vectors in E. coli based on the promoters and vectors that they used (Claims 60, 61, 67, and 68).

Claims ~~34~~, ~~49~~, 58, 60, 61, 65, 67, and 68 are rejected under 35 U.S.C. § 103 as being unpatentable over Riordan et al. (1989). The teachings of Riordan are discussed above. Riordan et al. discloses the cDNA for CFTR gene. This cDNA is 99% identical to that disclosed by the Applicants, with only a single base change and position 1990. The Applicants state on page 13 that their cDNA sequence is markedly different from the cDNA disclosed by Riordan et al. This is not the case because the Applicants admit that they have acquired the Riordan et al. clones from ATCC (page 10) and, in their 1990 paper published in Nature they state that the "DNA sequence analysis of the complete sequence revealed a sequence identical to that reported by Riordan et al., with the exception that the base at position 1990 is C rather that A". This single base change may be incidental. None-the-less, this changes the Applicants His to Asn at position 620, over 100 amino acids away from the known active region of CFTR at position 508. Therefore, the cDNA sequence encoding the CFTR gene is obvious over Riordan et al. because with only a single base difference between these two long sequences it would have been obvious to persons of ordinary skill in the art that the two sequences code for the same protein, that is, CFTR. Riordan et al. expressed the CFTR from epithelial cells; therein, it would have been obvious to a person of ordinary skill in the art that CFTR could be expressed from other mammalian cell lines such as CHO and C127.

Claims ~~30~~, ~~31~~, 99, and 100 are rejected under 35 U.S.C. § 103 as being unpatentable over Riordan et al. as applied to claims ~~34~~, ~~49~~, 60, 61, 65, 67, and 68 above, and further in view of Sambrook et al. (1989). Riordan et al. cloned the DNA from the region of the CF locus (page 1066, col. 2) to isolate the cDNA encoding the CFTR gene. Riordan et al. do not teach which phages or cosmids that they used to clone the cDNA, probably because cloning is a technique that is well-known and widely used in the art. However, Sambrook et al. teaches that bacteriophage lambda and cosmid vectors are routinely used for cloning DNA (page 9.4). Sambrook et al. also teaches that cosmids serve as vehicles to introduce the recombinant genomes into bacteria where that are propagated as large plasmids (Claim 2). In Chapter 16, Sambrook et al. teach the expression of proteins from cloned genes (pages 16.2+ and 16.30+; Claims 4, 5, 6, and 14). Taken together, it would have been obvious to one of ordinary skill in the art at the time the invention was made to insert the DNA into phages/plasmids and insert the compositions into cells because the cDNA was cloned in a phage or plasmid by Riordan et al. and Sambrook et al. teaches that cDNA can be used to transfect cells.

Claim ~~33~~ is rejected under 35 U.S.C. § 103 as being unpatentable over Riordan et al. and Sambrook et al. and further in view of Nichols (1988). Nichols (page 189) teaches that "children with diseases such as sickle cell anemia, cystic

fibrosis, thalassemia, and severe combined immune deficiency live longer that they did in the past, but their lives remain bound by restrictions imposed by their illnesses. Somatic cell gene therapy is one of several new therapeutics approaches that may help such children in the future. A child with a life-threatening but reversible genetic disease caused by a defect in a single gene would be treated with the gene's normal counterpart. The normal gene, provided through recombinant DNA technology, would be inserted into a specific tissue in the child's body and would not be passed on to future generations". With the disclosed cDNA sequence by Riordan et al. and the teachings of Sambrook et al. on how to transform eukaryotic cells to express proteins encoded by cDNA, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a therapeutic composition with the cDNA encoding CFTR. This concept is supported by Nichols who teaches that somatic cell gene therapy in which a product expressed by a normal gene would function in place of the defective gene product would be a viable method of treating cystic fibrosis.

Claims 25-27, 38, 39, 50-54, 59, 62, 66, and 100 are not anticipated or rendered obvious over Collins et al. Collins et al. do not teach the prevention of the expression of cDNA

encoding CFTR by introducing an intron into the cDNA or by introducing the sequence depicted in Fig. 6. Collins et al. do not suggest expressing CFTR in insect or plant cells, for example.

Claims 25, 27, 29, 36-46, 50-54, 59, and 66 are not anticipated or rendered obvious over primary teachings of Riordan et al. Riordan et al. do not teach the prevention of the expression of cDNA encoding CFTR or the sequence depicted in Fig. 6. Riordan et al. do not suggest expressing CFTR in insect or plant cells, for example.

Any inquiry concerning this communication should be directed to Karen Cochrane Carlson, Ph.D. at telephone number (703) 308-0034.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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GROUP 1800